PATENT
Attorney Docket No. **02481.1693**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
HABERMANN et al.	Group Art Unit: 1656
Application No.: 09/664,326	Examiner: Holly G. Schnizer
Filed: September 18, 2000	Confirmation No.: 4393
For: **SIGNAL SEQUENCES FOR PREPARING LEU-HIRUDIN BY SECRETION BY E. COLI INTO THE CULTURE MEDIUM**	

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed August 24, 2006, and further to Board Rule 41.37, Appellants present this brief and enclose herewith a check for the fee of $500.00 required under 37 C.F.R. § 1.17(c).

This Appeal Brief is being filed concurrently with a petition for an Extension of Time for Three months, and the appropriate fee.

This Appeal responds to the May 30, 2006, final rejection of claims 6-9.

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 06-0916.

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REAL PARTY IN INTEREST

Sanofi-Aventis Deutschland GmbH is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences, of which appellant, appellant's legal representative, or assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-5 and 10-14 stand cancelled without prejudice or disclaimer. Claims 6-9 stand finally rejected. Final Office Action mailed May 30, 2006. The list of claims on appeal are attached as an appendix to this appeal brief. (37 C.F.R. § 41.37(c)(1)(iii)).

STATUS OF AMENDMENTS

All amendments have been entered and considered at this time.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 6 is drawn to:

[a] process for selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein in *E. coli*, comprising:

(a) expressing in *E. coli* in culture medium, hirudin or a hirudin derivative which has antithrombotic activity, and which has a defined amino acid, aa_X, at its N terminus, wherein said amino acid is connected via its N-terminal to a test signal peptide;

(b) determining expression rate by measuring said hirudin or hirudin derivative activity in the culture supernatant;

(c) repeating steps (a) and (b) with various signal peptides;

(d) selecting said signal peptide by comparing the expression rates represented by the hirudin or hirudin derivative antithrombotic activity found in step (b)

wherein the E. coli bacteria are not E. coli secretor mutants.

The specification teaches that an aspect of the invention is "a process for finding a suitable signal peptide for [later] secretory expression of a desired protein in E. coli." (specification page 5, lines 21-23). The specification also discloses various working examples that illustrate the process of claim 6 (Examples 1-5 and 7-11, pages 7-17, *summarized in* Table 2).

Claims 7-9 depend from claim 6. Claim 7 is directed to the process of claim 6, wherein aa_x is leucine. *See also* specification at p. 6, lines 6-11. Claim 8 is drawn to the process of claim 6 further comprising expressing said signal peptide and the desired hirudin or hirudin derivative protein in E. coli via a nucleic acid construct, wherein expression of the desired hirudin or hirudin derivative protein and said signal peptide occurs with simultaneous elimination of said signal peptide. *Id.* Claim 9 is directed to

the process of claim 6, wherein the desired hirudin or hirudin derivative protein is hirudin. *See also* specification at p. 5, lines 11-18.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 6-9 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time that the application was filed (OA dated Dec. 29, 2005, page 3; FOA dated May 30, 2006, page 2).

ARGUMENT

Applicants were in possession of a process "wherein the E. coli bacteria are not E. coli secretor mutants" at the time of filing

Courts have expressed the test for compliance with the statutory written description requirement as, for example, "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter." (35 U.S.C. § 112, 1st paragraph (2005); *In re Kaslow,* 707 F.2d 1366, 1375 (Fed. Cir. 1983)). Applying the rule to the present case, the test is whether Applicants were in possession of a process for selecting a signal peptide for secretory expression, wherein the *E. coli* bacteria are not *E. coli* secretor mutants. The pertinent specification passage reads:

> Competent cells of the E. coli strain Mc1061, or the secretor mutant WCM100, were transformed with the ligation mixture and grown under selection pressure on ampicillin-containing plates. The next morning, expression as described in Example 6 was then compared with the Ala-hirudin expression using *E. coli* strain WCM100/pCM7053. It was found that the expression obtained was about 1.5 times better than in the comparative test. (Specification at p. 9, lines 1-6 (underlining added)).

The underlined portion of the passage clearly indicates that Applicants were in possession of methods wherein *both E. coli* strain Mc1061 (a non secretor mutant) *and* the secretor mutant WCM100 were used. As readily understood by one of ordinary skill, *E. coli* encompasses a genus of bacterial strains. Upon reading the underlined section, one of ordinary skill in the art would understand that Applicants contemplated using at least *E. coli* strain Mc1061 (non-secretory strain) and secretor mutants in the methods of the invention, and, therefore, were in possession of such methods.

The Examiner asserts that the specification *fails to* teach that *the type* of E. coli strain used *is important*, or more specifically, that non-secretor mutants *should be* used (OA dated Dec. 29, 2005 page 4, bridging paragraph). The Examiner then, incorrectly asserts that because the specification teaches that any E. coli could be used, the negative limitation of "not a secretor mutant of E. coli" is considered *new matter.* (*Id.*) However, whether or not the specification teaches that "non secretor mutants [of E. coli] *should be used"* is immaterial to the Applicant's possession of the claimed subject matter. The test for compliance with the written description only requires that the specification reasonably conveys to the skilled artisan that the inventor had possession of the claimed invention at the time of filing. *In re Kaslow,* 707 F.2d at 1375. The requirement is met here because the specification clearly demonstrates that Applicants were in possession of a method using both secretor and non-secretor E. coli strains.

A subgenus of E. coli bacteria that are not E. coli secretor mutants is fully supported by the specification.

The Office further argues that "while the specification may provide support for using the E. coli strain Mc1061 in the claimed method, it does not support using a genus of E. coli strains that are not secretor mutants." (FOA dated May 30, 2006 at page 3).

The disclosure in the working examples of *E. coli* strain Mc1061 (Specification at page 9, lines 1-6) is not the only disclosure of non-secretor mutants. As examples, Applicants cite the following specification passages:

> Another aspect of the invention is a process for preparing Leu-hirudin, in which...(b) the expression plasmid from (a) is expressed in a suitable *E. coli* cell. (Specification at page 5, lines 11-15).

> A further aspect of the invention is a process for finding a suitable signal peptide for secretory expression of any desired protein in *E. coli*. (Specification at page 5, lines 21-22).
>
> A process for selecting a suitable signal peptide for secretory expression of a desired protein in *E. coli*, comprising:
>
> (a) expressing in *E. coli* in culture medium, hirudin or a hirudin derivative which has antithrombotic activity, and which has a defined amino acid, aa_X, at its N terminus, wherein said amino acid aa_X is connected via its N-terminal to a signal peptide to be tested; (Specification, at claim 6, as originally filed).

These passages clearly convey to one of ordinary skill in the art that Applicants were in possession of methods wherein *E. coli* bacteria in general were used, regardless of whether the *E. coli* bacteria were, or were not, secretor mutants.

The amendment claiming a process "wherein the E. coli bacteria are not E. coli secretor mutants" is fully supported by the specification.

With respect to provisos, the MPEP teaches: "[a]ny . . . exclusionary proviso must have basis in the original disclosure; If alternative elements are positively recited in the specification, *they may be explicitly excluded* in the claims." (MPEP §2173.05(j) citing *In re Johnson*, 558 F.2d 1008, 1019 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.") The facts in the subject case square with those of *In re Johnson*. The *Johnson* specification taught a genus and several specific example species thereof. (Id. at 1019). Like *In re Johnson*, the subject specification teaches an E. coli genus and provides specific examples of species, for example secretor mutant WCM 100 and Mc1061, that can be used in the claimed invention. The relevant issue in *In re Johnson* was whether the specification of the parent application provided written description support for two exclusionary provisos

in the daughter application. (*Id.* at 1014) Each proviso excluded a *genus* of compounds from the scope of claim 1, which was directed to a broader genus of polyarylene polyethers. *Id.* at 1013; nn.12. Even though the provisos were never explicitly taught in the parent specification they were nonetheless found to be *properly supported* by the disclosure. (*Id.* at 1017). The court reasoned that "the [parent] specification supported the claims in the absence of the limitation, and that specification, having described the whole, necessarily described the part remaining." *Id.* at 1019. Notably, each of the genus-excluding provisos in *Johnson* was based on the disclosure of a *single* compound. (*Id.* at 1012-13). In accordance with *Johnson*, the subject specification fully supports the recitation "wherein the E. coli bacteria are not an E. coli secretor mutants" because the specification appropriately discloses the subject matter removed by the proviso.

The Office has already admitted that "the specification as a whole teaches that any E. coli strain could be used" in the methods of the invention. (FOA, dated May 30, 2006, at bottom of page 4, underlining added). Having described experiments where secretor mutants were used, (*see, e.g.*, the working Examples) Applicants carve out subject matter drawn to those secretor mutants from the pending claims. The propriety of this claim amendment is supported by the M.P.E.P. and case law. As explained before, based on *In re Johnson*, it has been recognized that inventors may claim less than the full scope of their disclosure and that "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." (M.P.E.P. § 2173.05(i) (citing *In re Johnson*, 558 F.2d at 1019)).

Upon reading the passage, "[c]ompetent cells of the E. coli strain Mc1061, or the secretor mutant WCM100, were transformed with the ligation mixture and grown . . .," one of ordinary skill in the art would clearly understand that secretor mutants can be used in the methods of the invention, and, therefore, that Applicants were in possession of such methods. Therefore, Applicants can properly exclude such subject matter from the claims and claim methods where the *E. coli* bacteria are not secretor mutants. (*Id.*) A more detailed analysis of the propriety of the proviso in the instant claims will be presented in the following sections.

Applicants teach a method using an E. Coli genus.

The original specification disclosed E. coli as the genus of cells for use in signal peptide testing, e.g., "expressing in E. coli in culture medium, hirudin or a hirudin derivative which has antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid is connected via its N-terminal to a test signal peptide. (original claim 6). "(a) hirudin . . . which has a defined amino acid . . .connected N-terminally to a signal peptide is expressed in E. coli." (specification page 5, lines 22-25). One of ordinary skill would readily recognize that any lab-safe E. coli straincould be used. Therein, the subject specification, like *Johnson*, teaches that any of a genus can be used. (FOA, dated May 30, 2006, at bottom of page 4 (*Examiner acknowledging teaching of any E. Coli*)). While *Johnson* further described the bounds of the genus, an elaborate description is not necessary for one ordinary skill in the subject case.

Exclusionary claim provisos are permitted to be broader than an originally disclosed species.

The specification in *In re Johnson* positively recited two species that served as the basis for two provisos that excluded subject matter *broader than* the original two species recited. (*Johnson* 558 F.2d at 1013, Fn 12). Like *Johnson*, the subject specification recites two alternative species of the E. coli genus for use in selecting a signal peptide (specification at page 9, lines 1-6).

The exclusionary claim limitation of *Johnson*, was intended to exclude two species, which the applicants discovered that they were not entitled to during prosecution. (*Johnson* 558 F.2d at 1018). In fact, more than the two species were excluded from the claimed subject matter; equivalent species were also excluded. (*Id.* 558 at 1013, Fn 12). Similar to *Johnson*, the proviso of claim 6 excludes secretor mutants, for example WCM100, which is taught in the specification as a specific example.

The court of *In re Johnson* explained, "[t]he notion that one who fully discloses and teaches those skilled in the art how to make and use a genus and numerous species there within, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result in hypertechnical application of legalistic prose relating to that provision of the statute." (*Id.* at 1019). The court of *In re Johnson* held that a claim to a genus with a recital of a negative proviso that did not appear in the specification *complied* with the description requirement. (*Id.* at

1008). It follows that the subject negative proviso also complies with the written description requirement.

The Examiner's reasoning is not supported by case law.

The Examiner appears to attempt to distinguish the facts of the subject application with the facts of *In re Johnson*, and identifies three factors as contributing to the asserted lack of written description. The Examiner argues that the specification fails to teach that *the type* of E. coli strain used *is important*. The Examiner argues more specifically that the specification fails to teach that non-secretor mutants *should be* used Further, the Examiner reasons that since the specification as a whole teaches that any E. coli strain could be used and that the type is not important to the invention, the negative limitation of not an E. coli secretor mutant is new matter (OA dated Dec. 29, 2005 page 4, bridging paragraph).

The standard does not include a teaching of importance.

Neither *Johnson* nor the current standard for written description require that the specification teach that the subject matter excluded by the provisos were important. Rather, the standard is whether Applicants were in possession of the claimed method wherein the *E. coli* bacteria are not *E. coli* secretor mutants. M.P.E.P. § 2163.02. As explained above, the standard has been met.

The proviso need not cover subject matter recommended for use.

The Examiner asserts that since the subject specification fails to teach that non-secretor mutants *should be* used, the negative limitation of "non-secretor mutants" is new matter. This conclusion is contrary to the holding of *In re Johnson*. *In re Johnson* does not hold that the negative proviso must be disclosed in the specification, much

less that the same need be recommended for use. Indeed, the entire issue in *In re Johnson* revolved around the fact that the specification *did not disclose explicitly that the excluded subject matter should not be part of the invention.* As mentioned above, the instant specification teaches that non-secretor mutants *can be* used in the claimed invention (p. 9, lines 1-6), which is all that is required to exclude the subject matter under *In re Johnson.*

The standard is whether Applicants were in possession of the claimed method.

Again, *In re Johnson*'s holding is at odds with the Examiner's assertion, where the Examiner asserts that since the specification as a whole teaches that *any* E. coli strain could be used and that the type is not important to the invention, the negative limitation of not an E. coli secretor mutant is new matter (OA dated Dec. 29, 2005 page 4, bridging paragraph). As discussed above, the subject original specification teaches the use of the E. coli genus., The *In re Johnson* specification explicitly teaches that the values of the variables excluded by the provisos (residuum E of the dihydric phenol of these alkali metal salts) *are not narrowly critical.* (*Johnson* 558 F.2d at 1011). The facts of *Johnson* square well with the facts of the subject case, where the specification teaches that *any* E. coli could be used (as admitted by the Examiner, (OA dated Dec. 29, 2005 page 4, bridging paragraph).

Case law applying application of the written description requirement to method claims supports patentability of the subject method claim

The courts have recognized the difference between providing written description support for a method claim that calls for the use of a genus of compounds (or in this case, bacterial strains) and a composition claim drawn to that same genus of

compounds (or bacterial strains). For example, the court in *In re Herschler* found that a single example disclosing a single corticosteroid in the solvent DSMO was sufficient written description support for a *method* of enhancing dermal penetration of a the genus of "physiologically active steroid[s]." *In re Herschler*, 591 F.2d 693, 701 (CCPA 1979). The court did not require the inventor to be in possession of all possible physiologically active steroids that could be used in his method, but that he be in possession of a method of enhancing penetration of an steroid. *Id.* The inventor found that DMSO enhances the penetration of a number of materials through the skin. *Id.* at 694. The inventor then claimed a *method* comprising administration of *a physiologically active steroidal agent* and an amount of DMSO sufficient o enhance penetration of said steroidal agent. The issue faced by the court was whether *Herschler's* application was entitled to the benefit of the filing date of a great grandparent application in order to obviate rejections based on intervening prior art. *Id.* at 696. *Herschler's* great grandparent application disclosed only one working example directed to steroids. That example described the treatment of a patient with dexamethasone 21-phosphate (a corticosteroid). *Id.* Corticosteroids are a subgenus of steroids. *Id.* The court concluded that the single example disclosing dexamethasone 21-phosphate provided sufficient written description for the method comprising administration of *a genus of steroidal agents*, because, although steroids have a broad scope of physiological activity, they are chemically similar with respect to penetration of the skin aided by DMSO. *Id.* at 701. The court stated that "[i]t is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure *that [applicants] invented*

processes including those limitations." *Id.*, emphasis added. The court summarized the issue as "would the worker of ordinary skill in this art consider 'steroidal agents' to be operative [in the method claim] when considering the great grandparent's disclosure?" *Id.* Because *Herschler's* great grandparent application adequately conveyed to one of ordinary skill in the art that steroids could be used in the method claimed, the court found that *Herschler* was entitled to the benefit of priority from the great grandparent application. *Id.*

The equivalent inquiry in the present case would be: would the worker of ordinary skill in this art consider *E.coli* that are not secretor mutants to be operative in a process for selecting a signal peptide for secretory expression of a protein in *E. coli*, when considering the application disclosure? The answer to the question is clearly affirmative. As mentioned before, the Office has already acknowledged that "the specification as a whole teaches that *any* E. coli strain could be used and is not important to the method of the invention." Office Action dated May 30, 2006, at bottom of p. 4 (emphasis added). The specification also teaches that both secretor mutants and non-secretor mutants can be used in the claimed invention. For example, the specification states that:

> Competent cells of the E. coli strain Mc1061, or the secretor mutant WCM100, were transformed with the ligation mixture and grown under selection pressure on ampicillin-containing plates.

Specification at p. 9, lines 1-3. This passage would clearly convey to one of ordinary skill in the art that *at least* the *E. coli* non-secretor mutant Mc1061 *and* the *E. coli* secretor mutant WCM100 are operative in the claimed invention. Because the claimed method involves a comparison of expression rates using different signal

peptides, one of ordinary skill in the art would understand that it is irrelevant whether secretor mutants or non-secretor mutants are used in the claimed method. Therefore, the specification as a whole, including working Examples 1-12, and Table 1, clearly conveys to one of ordinary skill in the art that both *E. coli* non-secretor mutants in general, *and E. coli* secretor mutants in general are operative in the claimed methods. As with the court in *In re Herschler*, which found that steroids behave similarly with respect to DMSO-mediated penetration of the skin, expression of the signal peptide recited in the claims occurs similarly in any type of *E. coli* bacteria, whether secretor mutant or not, and therefore, the type of *E. coli* bacteria in which the expression of the signal peptide occurs is not essential to the claimed invention. For these reasons, the amendment to claim 6 at issue in this appeal is fully supported by the specification.

This situation is also analogous to Example 18 of the USPTO training materials entitled "Synopsis of Application of Written Description Guidelines," available at http://www.uspto.gov/web/menu/written.pdf. The claim in Example 18 of the training materials is drawn to a method of expressing a protein in a particular mitochondria. The illustrative specification of Example 18 teaches the expression of a single protein using the mitochondria. The analysis section of the example indicates that, although the particular mitochondria is essential to the claimed method, a particular nucleic acid encoding for a specific protein is not. Therefore, it is not necessary to disclose all of the possible proteins that can be expressed in the mitochondria because one of ordinary skill in the art would know how to use the expression system based on the single disclosed embodiment and would recognize that Applicants were in possession of such methods.

In the instant case, as explained above, one of ordinary skill in the art would recognize from the specification that any *E. coli* bacteria, including *E. coli* that are not secretor mutants, can be used in the claimed methods. Moreover, the specific strain of *E. coli* non-secretor mutant used is not essential to the claimed methods. Therefore, one of ordinary skill in the art would recognize that Applicants were in possession of processes of selecting signal peptides wherein the *E. coli* bacteria are not *E. coli* secretor mutants. In light of the foregoing remarks, the Examiner's rejection should be reversed.

CONCLUSION

For the reasons given above, The subject matter of claim 6 complies with the written description requirement and the negative proviso is fully supported by the specification as originally filed. Therefore, pending claims 6-9 are allowable and reversal of the Examiner's rejection is respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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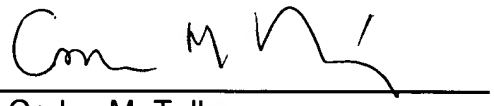
By: 

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Dated: February 15, 2007

Claims Appendix

CLAIMS ON APPEAL:

1-5. (Canceled)—For being directed to non-elected matter.

6. (Previously presented) A process for selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein in *E. coli*, comprising:

(a) expressing in *E. coli* in culture medium, hirudin or a hirudin derivative which has antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid is connected via its N-terminal to a test signal peptide;

(b) determining expression rate by measuring said hirudin or hirudin derivative activity in the culture supernatant;

(c) repeating steps (a) and (b) with various signal peptides;

(d) selecting said signal peptide by comparing the expression rates represented by the hirudin or hirudin derivative antithrombotic activity found in step (b)

wherein the E. coli bacteria are not E. coli secretor mutants.

7. (Previously presented) The process of claim 6, wherein aa_x is leucine.

8. (Previously presented) The process of claim 6, further comprising expressing said signal peptide and the desired hirudin or hirudin derivative protein in E. coli via a nucleic acid construct, wherein expression of the desired hirudin or hirudin derivative protein and said signal peptide occurs with simultaneous elimination of said signal peptide

wherein the E. coli bacteria are not E. coli secretor mutants.

9. (Previously presented) The process of claim 6, wherein the desired hirudin or hirudin derivative protein is hirudin.

10-14. (Canceled)—For being directed to non-elected matter.

Evidence Appendix

None.

Related Proceedings Appendix

None.